

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Error Remarks
1	BRS	L1	17475	macrophage	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/01/3 1 15:28		0	
2	BRS	L2	11385	glutathione or GSH	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/01/3 1 15:29		0	
3	BRS	L3	139	1 same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/01/3 1 15:29		0	
4	BRS	L4	2909	cachectic or cachexia	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/01/3 1 15:29		0	
5	BRS	L5	132317	cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/01/3 1 15:30		0	

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Errors	Errors
6	BRS	L6	1825	(cachectic or cachexia) same (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/01/31 15:31		0	
7	BRS	L7	7134	cystine	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/01/31 15:31		0	

Er ro r De fi ni ti on	Er ro rs	Com men ts	Time Stamp	DBs	Search Text	Hits	L #	Type
	0		2002/01/3 1 15:32	USPAT; US-PGPUB; EPO; JPO; DERWENT	((cachectic or cachexia) same (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease))) same cystine	3	L8	BRS
	0		2002/01/3 1 15:33	USPAT; US-PGPUB; EPO; JPO; DERWENT	((cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease))) same cystine	58	L9	BRS

Er ro r	Er ro rs	Com men ts	Time Stamp	DBs	Search Text	Hits	L #	Type
					(cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) same cystine disease))	58	L11	BRS
	0		2002/01/3 1 15:33	USPAT; US-PGPUB; EPO; JPO; DERWENT				
					(cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) same cystine disease))	2	L12	BRS
	0		2002/01/3 1 15:33	USPAT; US-PGPUB; EPO; JPO; DERWENT				

Er ro r De fi ni ti on	Er ro rs	Comments	Time Stamp	DBs	Search Text	Hits	L #	Type	
	0		2002/01/3 1 15:34	USPAT; US-PGPUB; EPO; JPO; DERWENT	((cachectic or cachexia) same (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease))) same 3	2	L14	BRS	13
	0		2002/01/3 1 15:34	USPAT; US-PGPUB; EPO; JPO; DERWENT	(cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) same 3	18	L13	BRS	14

> d his

(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT
14:53:49 ON

31 JAN 2002

L1 448179 S MACROPHAGE
L2 225702 S GLUTATHIONE OR GSH
L3 2653 S L1 (P) L2
L4 44743 S CYSTINE
L5 95 S L3 (P) L4
L6 1789 S CACHECTIC OR CHACHEXIA
L7 2386695 S CANCER OR DIABETES OR (GASTROINTESTINAL
INFLAMMATORY DISEASE)
L8 792 S L6 AND L7
L9 1 S L5 AND L8
L10 2 S L3 AND L8
L11 1 S L10 NOT L9
L12 164 S (L3 OR L5) AND L7
L13 7 S L12 AND L4
L14 4 DUPLICATE REMOVE L13 (3 DUPLICATES REMOVED)
L15 3 S L14 NOT L10

=> log y

CEP-HTM

FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002

=> file medline caplus biosis embase agricola
COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
0.15	0.15

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 14:53:49 ON 31 JAN 2002

FILE 'CAPLUS' ENTERED AT 14:53:49 ON 31 JAN 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 14:53:49 ON 31 JAN 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC. (R)

FILE 'EMBASE' ENTERED AT 14:53:49 ON 31 JAN 2002
COPYRIGHT (C) 2002 Elsevier Science B.V. All rights reserved.

FILE 'AGRICOLA' ENTERED AT 14:53:49 ON 31 JAN 2002

=> s macrophage
L1 448179 MACROPHAGE

=> s glutathione or GSH
L2 225702 GLUTATHIONE OR GSH

=> s l1 (p) l2
L3 2653 L1 (P) L2

=> s cystine
L4 44743 CYSTINE

=> s l3 (p) l4
L5 95 L3 (P) L4

=> s cachectic or chachexia
L6 1789 CACHECTIC OR CHACHEXIA

=> s cancer or diabetes or (gastrointestinal inflammatory disease) or
(chronic rheumatoid arthritis) or (hepatitis or (hepatic cirrhosis) or
(hypersensitive interstitial pneumonia) or (pulmonary fibrosis) or
(autoimmune inflammatory disease)
UNMATCHED LEFT PARENTHESIS 'OR (HEPATITIS'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s cancer or diabetes or (gastrointestinal inflammatory disease) or
(chronic rheumatoid arthritis) or hepatitis or (hepatic cirrhosis) or
(hypersensitive interstitial pneumonia) or (pulmonary fibrosis) or
(autoimmune inflammatory disease)
2 FILES SEARCHED...
3 FILES SEARCHED...
L7 2386695 CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY DISEASE)
OR (CHRONIC RHEUMATOID ARTHRITIS) OR HEPATITIS OR (HEPATIC
CIRRH

CEP-HTM

OSIS) OR (HYPERSENSITIVE INTERSTITIAL PNEUMONIA) OR (PULMONARY FIBROSIS) OR (AUTOIMMUNE INFLAMMATORY DISEASE)

=> s 16 and 17
L8 792 L6 AND L7

=> s 15 and 18
L9 1 L5 AND L8

=> d 19 1 ibib abs

L9 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:161498 CAPLUS

DOCUMENT NUMBER: 134:202694

TITLE: Method using a **cystine** derivative for suppressing immune responses and treating **cachectic** conditions by reducing intracellular content of **glutathione** in **macrophages** and monocytes

INVENTOR(S): Hamuro, Junji; Murata, Yukie

PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan

SOURCE: U.S., 26 pp., Cont.-in-part of U.S. Ser. No. 181,881.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6197749	B1	20010306	US 1999-334647	19990617
US 2001000784	A1	20010503	US 2000-731830	20001208
PRIORITY APPLN. INFO.:			US 1998-181881	A2 19981029
			JP 1997-312727	A 19971029
			JP 1998-308300	A 19981029
			US 1999-334647	A1 19990617

OTHER SOURCE(S): MARPAT 134:202694

AB A method of suppressing immune responses comprises administering to a patient in need thereof an effective amt. of a compn. comprising a substance capable of reducing the content of reductive **glutathione** in **macrophages**. Compds. of the invention include **cystine** derivs. A method for treating **cachectic** conditions is also disclosed.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

=> d his

(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT 14:53:49 ON 31 JAN 2002

L1 448179 S MACROPHAGE
L2 225702 S GLUTATHIONE OR GSH
L3 2653 S L1 (P) L2

CEP-HTM

L4 44743 S CYSTINE
L5 95 S L3 (P) L4
L6 1789 S CACHECTIC OR CHACHEXIA
L7 2386695 S CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY
DISEASE)
L8 792 S L6 AND L7
L9 1 S L5 AND L8

=> s l3 and l8

L10 2 L3 AND L8

=> s l10 not l9

L11 1 L10 NOT L9

=> d l11 1 ibib abs

L11 ANSWER 1 OF 1 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96170609 EMBASE

DOCUMENT NUMBER: 1996170609

TITLE: Lentinan regulates the local inflammatory cellular
reaction

at tumor tissues - Its relation with antitumor effects.

AUTHOR: Hamuro J.

CORPORATE SOURCE: Ajinomoto Co., Inc., Basic Research Institute, 1-1
Suzuki-cho, Kawasaki-ku, Kawasaki 210, Japan

SOURCE: Biotherapy, (1996) 10/4 (581-588).

ISSN: 0914-2223 CODEN: BITPE

COUNTRY: Japan

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer

026 Immunology, Serology and Transplantation

LANGUAGE: Japanese

SUMMARY LANGUAGE: English; Japanese

AB Either immunotherapy or chemotherapy requires anticachectic treatments to
improve its therapeutic effects leading to life prolongation. Cachexia is
mainly induced by oxidative local cellular inflammatory reactions at
tumor

tissues by production of PGE2, reactive oxygen intermediates and
cachectic/immunosuppressive cytokines such as IL-6, IL-1, TNF and
TGF- β . To induce the efficient specific immunological responses to
tumor antigens, it is necessary to induce cellular reactions at tumor
tissues to break the dormant state (ignorance of tumor antigens by host
immune systems). The induction of cellular reactions at tumor tissues is
confronted frequently with the conversion of cellular reactions into
oxidative inflammatory reactions via overactivation of **macrophages**
(M.ph.) and neutrophils. Lentinan suppresses the conversion and maintain
the redox state of M.ph. at the reduced state designated by the high
content of the reduced form of **glutathione (GSH)**.
M.ph.s with the high content of **GSH** respond to TH1 cytokines to
produce an increased amount of NO and a reduced amount of IL-6, whereas
M.ph.s with decreased **GSH** content respond in a manner resulting
in inverse effects. In the advanced stage of **cancer** patients,
the oxidative M.ph.s are responsible for the induction of TH2 cytokines
responses resulting in the induction of cachexia.

=> d his

CEP-HTM

(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT 14:53:49 ON
31 JAN 2002

L1 448179 S MACROPHAGE
L2 225702 S GLUTATHIONE OR GSH
L3 2653 S L1 (P) L2
L4 44743 S CYSTINE
L5 95 S L3 (P) L4
L6 1789 S CACHECTIC OR CHACHEXIA
L7 2386695 S CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY
DISEASE)
L8 792 S L6 AND L7
L9 1 S L5 AND L8
L10 2 S L3 AND L8
L11 1 S L10 NOT L9

=> s (l3 or l5) and l7
L12 164 (L3 OR L5) AND L7

=> s l12 and l4
L13 7 L12 AND L4

=> duplicate remove l13
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L13
L14 4 DUPLICATE REMOVE L13 (3 DUPLICATES REMOVED)

=> s l14 not l10
L15 3 L14 NOT L10

=> d l15 1-3 ibib abs

L15 ANSWER 1 OF 3 MEDLINE
ACCESSION NUMBER: 97407640 MEDLINE
DOCUMENT NUMBER: 97407640 PubMed ID: 9264389
TITLE: Increased **cystine** uptake capability associated
with malignant progression of Nb2 lymphoma cells.
AUTHOR: Gout P W; Kang Y J; Buckley D J; Bruchovsky N; Buckley A R
CORPORATE SOURCE: Department of Cancer Endocrinology, British Columbia
Cancer Agency, Vancouver, Canada.
CONTRACT NUMBER: DK44439 (NIDDK)
RR05407 (NCRR)
SOURCE: LEUKEMIA, (1997 Aug) 11 (8) 1329-37.
Journal code: LEU; 8704895. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 20000303
Entered Medline: 19970904

AB Analysis of rat, pre-T cell 'Nb2 lymphoma' sublines, manifesting
different
degrees of malignant progression, can indicate phenotypic changes

potentially useful as therapeutic targets. In this study, the prolactin (cytokine)-dependent Nb2-11 and autonomous Nb2-SFJCD1 sublines were compared for in vitro thiol growth requirements. Whereas Nb2-11 culture growth depended on 2-mercaptoethanol (2-ME; 33-100 microM), Nb2-SFJCD1 cells were 2-ME-independent. This difference stemmed from differential uptake of exogenous L-cystine, critically required for proliferation. Uptake of 35S-L-cystine (10 microCi/ml; 40 microM) showed Nb2-11 cells had low cystine uptake capability; 2-ME enhanced cystine uptake to growth-sustaining levels. Nb2-SFJCD1 cells did not require 2-ME due to intrinsic, 11-fold higher cystine uptake via the x(c)-cystine/glutamate transport system. In absence of 2-ME, monosodium glutamate abrogated Nb2-SFJCD1 proliferation by specifically inhibiting cystine uptake (85% at 10 mM). Elevated glutathione (GSH) levels were not essential for growth of either line as shown with L-buthionine-(S,R)-sulfoximine (0.1-4 mM) treatment. The cyst(e)ine requirement therefore

did

not primarily involve maintenance of normal GSH levels, reported critical for T lymphocyte replication. These and other results suggest increased cystine uptake capability constitutes another potential step in progression of T cell cancers which is not coupled to cytokine autonomy or metastatic ability development. The x(c)-transport system apparently provides a novel target for T cell cancer therapy. Its inhibition would suppress cystine uptake by certain progressed cells, and also interfere with cystine uptake, and subsequent cysteine release, by eg macrophages, thought to have a role in cysteine delivery to lymphoid cells.

L15 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:583141 CAPLUS
DOCUMENT NUMBER: 131:223492
TITLE: Immunomodulators for the treatment of immune diseases
INVENTOR(S): Hamuro, Junji; Murata, Yukie
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11246435	A2	19990914	JP 1998-308300	19981029
EP 1004302	A2	20000531	EP 1999-107480	19990429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001000784	A1	20010503	US 2000-731830	20001208
PRIORITY APPLN. INFO.:			JP 1997-312727	A 19971029
			JP 1998-308300	A 19981029
			US 1998-181881	A2 19981029
			US 1999-334647	A1 19990617

OTHER SOURCE(S): MARPAT 131:223492

AB This invention relates to a method for the treatment of immune diseases by

oral administration of immunomodulators which change oxidative and reductive conditions of macrophages and monocytes. **Cystine**

derivs. are effective for the improvement of conditions such as cachexia, **diabetes**, digestive tract inflammation, and **autoimmune inflammatory diseases**.

L15 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1992:347942 BIOSIS
 DOCUMENT NUMBER: BA94:40167
 TITLE: DYSREGULATION OF PLASMA AMINO ACID LEVELS IN HIV-INFECTION AND **CANCER** AND ITS RELEVANCE FOR THE IMMUNE SYSTEM.
 AUTHOR(S): DROEGE W; ECK H P; GMUENDER H; MIHM S
 CORPORATE SOURCE: DIV. IMMUNOCHEM., INST. IMMUNOL. GENETICS, DEUTSCHES KREBSFORSCHUNGSZENTRUM, D-W-6900 HEIDELBERG, GER.
 SOURCE: AMINO ACIDS (VIENNA), (1991) 1 (2), 193-198.
 CODEN: AACIE6.
 FILE SEGMENT: BA; OLD
 LANGUAGE: English

AB T cells have a weak membrane transport activity for **cystine** but strong transport activity for cysteine. Even moderate variations of the cysteine concentration affect T cell functions in spite of the high concentration of **cystine** in cultures with physiological amino acid concentrations. The IL-2 dependent DNA synthesis and the activation of cytotoxic T cells are positively regulated by cysteine, while the activity of the transcription factor NF.kappa.B and the production of

IL-2 are stimulated by active oxygen species and inhibited by cysteine or **GSH**. **Macrophages**, in contrast to T cells, take up more **cystine** than they need and release the excess after intracellular reduction as cysteine into the extracellular space. This "cysteine pumping activity" of **macrophages** raises intracellular **GSH** levels and DNA synthesis of T cells in the vicinity. The difference between the **cystine** transport activities of T cells and **macrophages**, therefore, enables T cells to switch between prooxidant and antioxidant states. The "cysteine pump" favors selectively the antigen-specific T cells that are about to be stimulated by antigen-presenting **macrophages**. The capacity of **macrophages** to take up **cystine** and to release cysteine is inhibited, however, by elevated extracellular glutamate concentrations.

Elevated plasma glutamate levels have been found in several pathological conditions including **cancer** and HIV-infection. In HIV-infected patients, the hyperglutamataemia is aggravated by hypocystinaemia and hypocysteinaemia. Our studies, therefore, suggest that the cysteine supply is impaired in several pathological conditions with immunodeficiencies including AIDS. N-acetyl-cysteine (NAC) is a safe and well established drug that may be considered for the treatment of patients with HIV-infection.

=> d his

(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT 14:53:49 ON 31 JAN 2002

L1 448179 S MACROPHAGE

CEP-HTM

L2 225702 S GLUTATHIONE OR GSH
L3 2653 S L1 (P) L2
L4 44743 S CYSTINE
L5 95 S L3 (P) L4
L6 1789 S CACHECTIC OR CHACHEXIA
L7 2386695 S CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY
DISEASE)
L8 792 S L6 AND L7
L9 1 S L5 AND L8
L10 2 S L3 AND L8
L11 1 S L10 NOT L9
L12 164 S (L3 OR L5) AND L7
L13 7 S L12 AND L4
L14 4 DUPLICATE REMOVE L13 (3 DUPLICATES REMOVED)
L15 3 S L14 NOT L10

=> log y

COST IN U.S. DOLLARS

SINCE FILE
ENTRY

TOTAL
SESSION

FULL ESTIMATED COST

65.72

65.87

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE
ENTRY

TOTAL
SESSION

CA SUBSCRIBER PRICE

-1.24

-1.24

STN INTERNATIONAL LOGOFF AT 15:09:53 ON 31 JAN 2002